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For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

(54) Title: OX40R BINDING AGENTS

(57) Abstract: The present invention discloses peptides isolated from the extracellular domain of OX40 Ligand (OX40L) capable of binding OX40 Receptor (OX40R) and inhibiting OX40R-OX40L interaction. Such peptides, fusion proteins comprising them, as well as peptides and other molecules designed on their sequences, can be used as OX40R binding agents competing with natural OX40L for blocking OX40R-mediated cell signaling in the prophylaxis and/or treatment of diseases related to activated T cells.

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INTERNATIONAL SEARCH REPORT

Inte Application No
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A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07K14/52 C07K14/705 C12N15/28 C12N5/10 C12N15/63
G01N33/53 A61K38/00 A61P31/00 A61P35/00 A61P37/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07K C12N G01N A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>WO 95 21915 A (UNIV LELAND STANFORD JUNIOR (US)) 17 August 1995 (1995-08-17) cited in the application page 27, line 22 -page 28, line 6 page 38, line 19 -page 39, line 9 page 42, line 12 - line 28 page 63, line 10 -page 65, line 16 --- -/--</p>	<p>1-8, 10-33</p>

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

A document defining the general state of the art which is not considered to be of particular relevance

E earlier document but published on or after the international filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

G document member of the same patent family

Date of the actual completion of the international search

23 September 2003

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Name and mailing address of the ISA

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/50089

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>DATABASE GSP 'Online! 23 January 2002 (2002-01-23) PENN S.G. ET AL.: "Protein #5114 encoded by probe for measuring heart cell gene expression" Database accession no. ABB23115 XP002211957 abstract</p>	4,6-8, 10-14, 16,17
X	<p>-& WO 01 57274 A (MOLECULAR DYNAMICS) 9 August 2001 (2001-08-09)</p> <p>SEQ ID NO:24885</p>	4,6-8, 10-14, 16,17
X	<p>-----</p> <p>DATABASE GSP 'Online! 12 February 2001 (2001-02-12) ROSEN C.A. ET AL.: "Human seretted protein sequence encoded by gene 39 SEQ ID NO:99" Database accession no. AAB44733 XP002211958 abstract</p>	4,6-8, 10-14, 16-18, 21-24, 30-33
X	<p>-& WO 00 58494 A (HUMAN GENOME SCIENCE INC.) 5 October 2000 (2000-10-05)</p> <p>SEQ ID NO:99 page 47 page 34, line 15 - line 28</p>	4,6-8, 10-14, 16-18, 21-24, 30-33
X	<p>-----</p> <p>DATABASE SWALL 'Online! 15 December 1998 (1998-12-15) ISONO T. ET AL.: "Expression of OX40 and OX40 ligand genes in rabbit HTLV-I-transformed T cell" Database accession no. 002765 XP002211959 abstract</p>	4,6,8, 11-14
X	<p>-----</p> <p>ALLIGNET J ET AL: "Sequence of a staphylococcal plasmid gene, vga, encoding a putative ATP-binding protein involved in resistance to virginiamycin A-like antibiotics" GENE, ELSEVIER BIOMEDICAL PRESS. AMSTERDAM, NL, vol. 117, 1992, pages 45-51, XP002083993 ISSN: 0378-1119 figure 3</p> <p style="text-align: center;">----- -/--</p>	4,6,8, 11-14

INTERNATIONAL SEARCH REPORT

Int'l Application No
PCT/EP 03/50089

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
T	DATABASE GSP 'Online! 18 June 2002 (2002-06-18) BEASLEY J. ET AL.: "Insulin/insulin-like growth factor receptor-binding peptide #1955" Database accession no. AAU89999 XP002211956 abstract	4,6,8
X	-& WO 01 72771 A (DGI BIOTECHNOLOGIES LLC.; NOVO NORDISC AS) 4 October 2001 (2001-10-04) SEQ ID NO:1428	4,6,8
A	WEINBERG A D: "OX40: targeted immunotherapy - implications for tempering autoimmunity and enhancing vaccines" TRENDS IN IMMUNOLOGY, ELSEVIER, CAMBRIDGE, GB, vol. 23, no. 2, 1 February 2002 (2002-02-01), pages 102-109, XP004347862 ISSN: 1471-4906 the whole document	1-8, 10-33
A	BODMER J.-L. ET AL.: "The molecular architecture of the TNF superfamily" TRENDS IN BIOCHEMICAL SCIENCES, vol. 27, no. 1, January 2002 (2002-01), pages 19-26, XP002211955 the whole document	1-8, 10-33
A	STÜBER ECKHARD ET AL: "The T cell-B cell interaction via OX40-OX40L is necessary for the T cell-dependent humoral immune response." JOURNAL OF EXPERIMENTAL MEDICINE, vol. 183, no. 3, 1996, pages 979-989, XP002255329 ISSN: 0022-1007 cited in the application page 980, column 2, line 3 - line 10 page 983, column 2, paragraph 2 - paragraph 3	1-8, 10-33

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 03/50089

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Insofar as claims 19 to 21 and 30 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☒ Claims Nos.: 9,34 (no search); 2,5 (incomplete search)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 9,34 (no search); 2,5 (incomplete search)

Present claims 2 and 5 relate to an extremely large number of possible OX40R binding agents. Support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the binding agents claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the OX40R binding agents as defined in claim 1 and on page 7, 1. 24 to p. 8. 1.2

Present claim 9 relates to an extremely large number of possible OX40R binding agents. In fact, the claims contain so many options, variables and possible permutations that a lack of clarity and conciseness within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible. Consequently, no search has been carried out for subject-matter of claim 9.

Further, present claim 34 relates to an extremely large number of possible kits for screening compounds. In fact, the claim contains so many options, variables and possible permutations that a lack of clarity and conciseness within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claim impossible. Consequently, no search has been carried out for subject-matter of claim 34.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

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Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9521915	A	17-08-1995	US 6242566 B1	05-06-2001
			AU 1583695 A	29-08-1995
			CA 2183066 A1	17-08-1995
			EP 0741784 A1	13-11-1996
			WO 9521915 A1	17-08-1995
			JP 9509826 T	07-10-1997
			US 2003149247 A1	07-08-2003
			US 2001044523 A1	22-11-2001
			US 2002077460 A1	20-06-2002
			US 6156878 A	05-12-2000
WO 0157274	A	09-08-2001	AU 3087801 A	14-08-2001
			AU 3087901 A	14-08-2001
			AU 3088001 A	14-08-2001
			AU 3088101 A	14-08-2001
			AU 3088201 A	14-08-2001
			AU 3088301 A	14-08-2001
			AU 3275701 A	14-08-2001
			AU 3275801 A	20-11-2001
			AU 3275901 A	14-08-2001
			AU 3276001 A	14-08-2001
			AU 3311401 A	14-08-2001
			AU 3658901 A	14-08-2001
			AU 6343201 A	11-12-2001
			AU 9295701 A	02-04-2002
			EP 1309723 A2	14-05-2003
			EP 1309724 A2	14-05-2003
			EP 1292704 A2	19-03-2003
			EP 1325149 A2	09-07-2003
			EP 1292705 A2	19-03-2003
			EP 1290216 A2	12-03-2003
			EP 1341930 A2	10-09-2003
			EP 1332224 A2	06-08-2003
			EP 1325150 A2	09-07-2003
			EP 1309725 A2	14-05-2003
			EP 1290217 A2	12-03-2003
			GB 2361238 A ,B	17-10-2001
			GB 2373500 A	25-09-2002
			GB 2374929 A	30-10-2002
			GB 2383043 A	18-06-2003
			GB 2375539 A	20-11-2002
			GB 2375111 A	06-11-2002
			GB 2374872 A	30-10-2002
			GB 2378754 A	19-02-2003
			GB 2382814 A	11-06-2003
			GB 2385053 A	13-08-2003
			GB 2376018 A	04-12-2002
			GB 2376237 A	11-12-2002
			GB 2380197 A	02-04-2003
			WO 0157270 A2	09-08-2001
			WO 0157271 A2	09-08-2001
			WO 0157272 A2	09-08-2001
			WO 0157273 A2	09-08-2001
			WO 0186003 A2	15-11-2001
			WO 0157274 A2	09-08-2001
			WO 0157275 A2	09-08-2001
			WO 0157276 A2	09-08-2001
			WO 0157277 A2	09-08-2001

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 03/50089

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 0157274	A		WO 0157278 A2	09-08-2001
			WO 0157251 A2	09-08-2001
			WO 0157252 A2	09-08-2001
WO 0058494	A	05-10-2000	AU 3908600 A	16-10-2000
			CA 2368719 A1	05-10-2000
			EP 1171626 A1	16-01-2002
			JP 2002539841 T	26-11-2002
			WO 0058494 A1	05-10-2000
WO 0172771	A	04-10-2001	WO 0172771 A2	04-10-2001
			AU 3930900 A	08-10-2001
			CA 2402780 A1	04-10-2001